REMARKS

After the claim amendments filed in Applicant's response of Dec. 13, 2005, claims 17, 20-23, 28-30, 41-43, 59-61, 63-65, 68-74, 82, 89-92, 140-148, 150-164 were pending in this case. This response cancels claims 20, 82, 151-155 and 164 without prejudice. Claims 28, 41, 42 90, 91, 144, 150, 159-161 are amended. No new claims have been added. With this amendment claims 17, 21-23, 28-30, 43, 59-61, 63-65, 68-74, 89-92, 140-148, 150, 156-163 are pending. Claims 43, 61, 63, 65, 69, 70, 89, 156 are withdrawn. None of these amendments constitute the addition of new matter.

Claim Amendments

Claims 28, 144 and 159 are amended to clarify that the claimed invention is for methods of inducing intracellular signals which induce "cellular chemotaxis." Support for this amendment is found throughout the specification, including at page 28, line 10 - page 29, line 7; page 39, lines 17-31; original claims 6, 9 and 25. With this amendment, all pending claims are directed to methods for inducing the release of an intacellular signal to induce cellular chemotaxis.

Claim 28 is further amended by reciting a chemical structure of the multivalent ligand found in originally presented claim 82. Claim 82 is accordingly canceled as redundant in view of the amendment to claim 28. With this amendment, all pending claims are directed to methods for inducing cellular chemotaxis by using a multivalent ligand having a specific structure.

Claims 41 and 42 are amended to conform to the amendment made in claim 28, where the biological response is cellular chemotaxis.

Claims 90 and 91 are amended to depend for claim 28.

Claim 91 is amended to change the dependency from canceled claim 82 to amended claim 28.

Claim 150 is amended to correct a typographical error by deleting the repeated term "wherein".

Claims 160 and 161 are amended to depend from claim 159.

Claim Objections

14. Claim 161 was objected to under 37 CFR 1.75(c) for failing to further limit the subject matter of a previous claim. Claim 161 is amended to depend from 159. Claim 159 recites a limitation to Z.

Maintained and New Claim Rejections

15. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140, 142, 143, 148, 150-157, and 162-164 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The Office Action states this is a rejection for new matter, alleging "the specification as filed does not appear to provide support for methods comprising signal recognition elements that are an N-formy or N-acyl peptide, which induces the release of an intracellular signal." Applicants respectfully traverse this rejection with respect to the claims as amended.

The claimed invention as amended is directed to methods of inducing intracellular signals which induce cellular chemotaxis. The specification provides support for the limitation of cellular chemotaxis at, for example, page 15, lines 13-31; Figs. 3-4; originally-filed claim 6.

Support for cellular chemotaxis induction by intracellular signals is found, for example, in the paragraph beginning at line 20 of page 18 ("A multivalent ligand can be involved ***directly*** in signaling where SREs on the multivalent ligand bind to cell surface receptors, similar to monomeric ligands, and directly induce (or inhibit) a response." (emphasis added) lines 21-23). Such direct signaling is by an intracellular signal. Ligand-mediated binding to a cell-surface receptor is known in the art to be regulated by release of an intracellular signal, such as by Ca^{2+} for example. The specification (page 29, lines 2-11) notes that chemotaxis is controlled, at least in part, by intracellular signaling ("These factors

[responsible for biofilm formation dependent on chemotaxis] control signal transduction pathways . . ."). Furthermore, in the Examples section, bacterial chemotaxis is noted as being well-studied with chemoattractants regulating chemotaxis by binding to specific receptors of the bacterial cell wall (page 34, lines 1-6). As noted, binding to cell membrane receptors results in generation of an intracellular signal that mediates a cellular response (e.g., chemotaxis) to such binding. With respect to intracellular signaling and chemotaxis of the presently claimed invention, for example, the intracellular signal can result in "changes in lateral clustering of the chemoreceptors" (page 34, lines 19-21). The ligand valency of the multivalent ligands of the present invention is demonstrated to affect "chemotactic activity" (page 35, lines 19-21: "The observed differences in concentration of maximum activity between the monomer **1** and multivalent **3** demonstrate that ligand valency affects chemotactic activity.")

Mammalian cells, such as neutrophils, similarly are capable of binding a chemoattractant, such as N-formyl peptide, to a cell-surface receptor and undergo chemotaxis via intracellular signaling (see "Modulation of Neutrophil Chemotaxis beginning on page 39, line 16). The specification implicitly recognizes that neutrophils respond to both intracellular and intercellular signals when undergoing chemotaxis ("In addition, and also in response to such chemoattractants neutrophils release intercellular signals that affect response in other cells . . . " page 39, lines 23-25).

For these reasons, it is believed that the amended claims meet the written description requirement and Applicant respectfully requests reconsideration and withdrawl of this rejection.

16. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140-148, 150-155, 157-160, and 162-164 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement The Office Action states this is a rejection for lack of written description. It is alleged that "only the methods comprising specific multivalent ligands that bind to cellular

receptors to induce chemotaxis or agglutination, as taught by the instant specification . . . meets the written description provision."

To facilitate prosecution, Applicants have amended the claims to clarify that the invention is for inducing intracellular signals which induce "cellular chemotaxis." In addition, Applicants have further amended claim 28 to provide detailed chemical structure of the multivalent ligand. Because all pending claims are directed to inducing intracellular signal release to induce cellular chemotaxis using specific multivalent ligands having N-formyl peptide or N-acyl peptide, Applicants assert the claims as amended meet the written description provision. Applicant respectfully requests this rejection be withdrawn.

Maintained Claim Rejections – 35 USC § 103

17. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 66, 68, 71-74, 82, 83, 90-92, 140-143, 144, 148, 150, 151, 154, 155, 157, 159 and 162-164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al. (WO 98/46270), Arimoto et al. (Chem. Commun., July 1999, Vol. 05, 1361-62) and further in view of Painter et al. (J. Cell. Biol. 1987, vol. 105, 2959-71). This rejection was maintained as set forth in the previous Office Action. Applicants traverse this rejection in view of the claim amendments and arguments presented herein.

The results achieved by the presently claimed invention are unexpected. The combination of Whitesides, Arimoto and Painter do not teach or suggest the presently claimed invention of inducing an intracellular signal which induces cellular chemotaxis using multivalent ligands containing N-formyl or N-acyl peptides. Applicants emphasize that the disclosure in Painter is for ***isolated*** N-formylated peptide binding neutrophil receptor. There is no teaching or suggestion that N-formylated peptide ***bound*** to a molecular scaffold, including the molecular scaffold structures of the claimed invention, is able to induce cellular chemotaxis. It is important to distinguish between an unbound chemotactic agent and bound chemotactic agent, especially in view of the role chemotactic chemical gradients play in modulating cellular chemotaxis.

The Office Action apparently alleges that one or both of Whitesides and Arimoto teaches that an N-formylated peptide bound to a molecular scaffold could induce cellular chemotaxis. Whitesides, however, does not provide any evidence that cellular chemotaxis can be induced using multivalent ligands where the signal recognition element is a peptide. Instead, Whitesides provides general speculation about presenting a polymer containing multiple copies of an active species. Similarly, Arimoto does not provide any indication that an N-formylated peptide bound to a molecular scaffold can induce cellular chemotaxis. Arimoto, rather, is confined to using a multi-valent polymer of vancomycin to enhance antibacterial activity. In view of the amendments to the claimed invention and the arguments presented, Applicants request this obviousness rejection be reconsidered and withdrawn.

New Claim Rejections – 35 USC § 103

18. Claims 17, 21, 22, 28-30, 41, 42, 59, 60, 64, 66, 68, 74, 82, 90-92, 142, 143, 144, 150, 151, 154, 155, and 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al. (Chem & Biol, vol. 7: 9-16, 2000) in view of Schiffman et al. (U.S. Pat. No. 4,427,660). Applicants traverse this rejection in view of the claim amendments and arguments presented herein.

Applicants have amended the claims to recite inducing an intracellular signal which induces cellular chemotaxis by introducing a multivalent ligand having an N-formyl or N-acyl peptide. Gordon describes multivalent ligand binding of L-selectin. The Office Action acknowledges that "Gordon et al. does not disclose N-formyl peptides" and so, accordingly, does not disclose N-formyl peptides bound to multivalent ligands to induce cellular chemotaxis. The Office Action alleges that Schiffman teaches the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils and that one of ordinary skill in the art would have been motivated to use N-formyl peptides as part of a multivalent system. Applicant respectfully disagrees with this interpretation. Schiffman attaches N-formyl peptides to antibiotics, and not to a multivalent

ligand structure as claimed in the present invention. First, there is no expectation of success that binding N-formyl peptides to a multivalent ligand would result in functional induction of cellular chemotaxis. There is a fundamental difference in attaching a chemotactic agent to an antibiotic, as was done in Schiffman, instead of to a multivalent ligand of the present invention. Schiffman acknowledges that antibiotics can themselves be chemotactic agents (column 5, lines 49-52). The unbound multivalent ligands of the presently claimed invention, in contrast, are not chemotactic agents. Accordingly, one of ordinary skill in the art would not expect binding a chemotactic agent to the claimed multivalent ligand structures would successfully induce cellular chemotaxis.

Second, the rational in Schiffman is to produce "bifunctional pharmaceuticals" (col. 6, line 15) (e.g. an antibiotic and an enhanced chemoattractant). Because the presently claimed invention is to induce a single biological function (cellular chemotaxis) there is no motivation to combine Schiffman with Gordon to generate an N-formyl peptide bound to the multivalent ligands disclosed in Gordon. In view of the amendments to the claimed invention and the arguments presented, Applicants request this obviousness rejection be reconsidered and withdrawn.

19. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140-143, 151, 154, 155, and 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides in view of Schiffman. For the reasons previously presented, including Whitesides only generally discussing biological responses, and the fact that Schiffman attaches N-formyl to an antibiotic without any teaching or suggestion by either Whitesides or Schiffman that N-formyl peptides attached to a multivalent ligand of the present invention is capable of inducing cellular chemotaxis, Applicants request this obviousness rejection be reconsidered and withdrawn.

20. Claims 17, 21-23, 28, 82, and 90 are rejected under 35 U.S.C. 103(a) as

being unpatentable over Kiessling (U.S. Pat. No. 6,291,616) in view of Schiffman. There is no teaching or suggestion, in either Kiessling or Schiffman, that cellular chemotaxis can be induced by presenting a multivalent ligand having a signal recognition element that is N-formyl peptide or N-acyl peptide. Schiffman is instead directed toward a bifunctional pharmaceutical wherein an antibiotic is attached to a chemotactic agent. There is no indication in either Schiffman or in Kiessling, that the claimed multivalent ligands having N-formyl or N-acyl peptide would induce cellular chemotaxis. Applicants request this obviousness rejection be reconsidered and withdrawn in view of the arguments and amendments made herein.

21. Claims 17, 21-23, 28, 59, 60, 64, 68, 74, 82, 90-92, 144, 148, 150, 154, 155, 157, 159, 162-164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arimoto in view of Schiffman. Arimoto teaches use of a polymer having multiple vancomycin residues to enhance antibacterial activity. Schiffman teaches attaching chemotactic agents to an antibiotic to make a bifunctional pharmaceutical. Neither Arimoto nor Schiffman, alone or in combination, teach or suggest use of the multivalent ligands having N-acyl or N-formal signal recognition elements to induce an intracellular signal which induces cellular chemotaxis. Applicants request this obviousness rejection be reconsidered and withdrawn in view of the arguments and amendments made herein.

22. Claims 17, 21-23, 28, 59, 60, 64, 68, 74, 82, 90-92, 144, 148, 150, 152, 154-157, 159, 162-164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanai in view of Schiffman. Kanai is concerned with interference of erythrocyte agglutination. For the reasons previously presented, namely the fact that Schiffman attaches chemoattractants to an antibody to obtain bifunctional pharmaceuticals, and Kanai is for a single functional pharmaceutical, a person skilled in the art would not combine the references in

the manner suggested by the Office Action. In addition, there is no indication that a chemoattractant bound to a multivalent ligand that is not an antibiotic would induce chemotaxis in a similar manner to a chemoattractant bound to an antibiotic. Accordingly, the cited references, alone or in combination, do not teach a chemoattractant bound to the multivalent ligands of the presently claimed invention that is capable of inducing an intracellular signal which induces cellular chemotaxis. Applicants request this obviousness rejection be reconsidered and withdrawn in view of the arguments and amendments made herein.

CONCLUSIONS

It is believed that the amendments and arguments presented herein address all outstanding objections and rejections made in the Office Action. It is believed that the claims as amended are patentable over the prior art cited and that the application meets the written description requirement with respect to the claims as amended. Applicant believes the claims as amended are allowable and requests the application be passed to issuance.

This amendment has not added any additional claims or any independent claims. No fees for excess claims are believed to be due. Applicant thanks the Examiner for the Communication of 12/27/06 which presents a one-month shortened deadline for responding. As this response is within the one-month deadline, Applicant believes no fees are due at this time. Should fees be due with this submission, please charge the appropriate fee(s) to deposit account 07-1969.

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